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10/530,171	05/17/2005	Youko Hirakawa	235054	9015

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LEYDIG VOIT & MAYER, LTD
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6731

EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,171	HIRAKAWA ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *12-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/27/05 and 12/21/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-35 are all the pending claims for this application.

Election/Restrictions

2. Applicant's election with traverse of Group I (Claims 1-11) in the reply filed on 2/2/07 is acknowledged. The traversal is on the ground(s) that searching claims of Group I for prior art "would likely uncover references that would otherwise be considered during examination of Groups II and III" and "no undue search [is incurred] in examining all the pending claims at the same time".

This is not found persuasive, because the claims do not satisfy unity of invention under § 1.475: each group lacks unity with each other group because there is no single general inventive concept specifically describing the unique special technical feature in each group (i.e., a cell-surface exposed antigen at the formation of a tumor mass). This is because the instant claims do not recite one common or corresponding special technical feature(s) that define the contribution which each claimed invention of Groups I-III, considered as a whole, makes over the prior art (see Chiavegato et al.; cited in the PTO-form 892 of 1/11/07). Applicants have not addressed this aspect of the Examiner's determination insofar as whether the claimed technical feature is a contribution over Chiavegato. Applicants are also reminded that an Examiner is not required to establish a search burden in finding lack of unity much less where a lack of unity restriction is required. Chapter 1800 of the MPEP does not speak to this issue.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 12-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups II and III, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/2/07.

4. Claims 1-11 are all the pending claims under examination.

Information Disclosure Statement

5. The international and foreign patent literature and the non-patent literature references cited in the IDS' of 4/27/05 and 12/21/05 have been considered and entered.

Specification

6. The use of the trademark e.g., Vectastain Elite ABC has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicants are advised to carefully check the entire specification for any other trademarks or tradenames that may not be properly identified.

Claim Objections

7. Claim 10 is objected to for the recitation "in the Sequence Listing" because the phrase does not further define the subject matter with respect to what is inherent to the sequence identifier for SEQ ID NO:17.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1-9 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-9 are drawn to any antigen exposed on a cell surface at the formation of a tumor mass which reads on the antigen per se which is found in nature. Products of nature do not constitute patentable subject matter as defined in 35 U.S.C. 101. See MPEP 2105. Since the antigen does not exist in nature in purified form, it is suggested that Applicants use the language "isolated" or purified" in connection with the antigen to identify a product that is not found in nature, provided support for such claim language can be found in the specification as originally filed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1-11 are indefinite for the recitation "at the formation of a tumor mass" in claim 1 because it is not clear if the exposed part of the antigen on the cell or any part of the cell is positioned at the formation of the tumor mass.

b) The recitation "the solid tumor" lacks antecedent basis in Claims 3 and 4. The preceding claim, Claim 1, is drawn to a "tumor mass."

c) Claims 3 and 4 are indefinite because it is not clear what the relationship is between the amount of antigen being measured on the solid tumor and the cultured solid tumor cell. Are Applicants comparing the level of antigen expression for a solid tumor cell in situ versus that expressed on a cell obtained from the solid tumor and cultured in vitro? Further it is not clear what is meant by the phrase "the existing amount", because the phrase implies some amount of antigen at a point or time relative to the amount expressed by the cultured solid tumor cell.

d) The recitation "the cell surface" lacks antecedent basis in Claim 4. The preceding claim, Claim 1, is drawn to "the surface of a cell."

e) Claim 10 is indefinite for the recitation "N-terminal of SEQ ID NO:17" because residues 600-1,960 of SEQ ID NO:17 comprise the C-terminal domain of the protein.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

10. Claims 5-9 are rejected under 35 U.S.C. 112, first paragraph, because the claims encompass subject matter that is not supported by the original disclosure of the specification.

Claims 5-9 are drawn to genii of mutant proteins for a cytoskeleton protein (Claim 5), a myosin protein (Claim 6), and a non-muscular myosin heavy chain type A protein (Claims 7-9). The only support in the specification for any mutant forms of these proteins is found at [0061], where "examples of the mutant include those which have amino acid sequences in which one or several amino acids are deleted, substituted or added, or those in which three-dimensional structure of the normal protein is modified." Further, the specification does not contemplate which of any mutations for these families of proteins would confer the properties on the protein of 1) being antigenic, 2) having a part exposed on a cell surface, and c) being expressed on a cell at the formation of a tumor mass (Claim 1).

Applicants have identified a single antibody-reactive protein, namely, non-muscular myosin heavy chain type A (NMMHC IIA; SEQ ID NO:17), which meets the criteria 1)-3) above. Thus one skilled in the art at the time of application filing in considering the instant claims would reasonably conclude that Applicants were not in

possession of the myriad mutant protein forms for cytoskeletal, myosin and NMMHC IIA proteins based on the written disclosure of the specification alone.

Enablement

11. Claims 5-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the full length non-muscular myosin heavy chain type A (NMMHC IIA) and genetically engineered truncations comprising residues 600-1,960 of SEQ ID NO: 17 and peptides of SEQ ID NOs: 20, 21 and 22 being antigenic and exposed on the cell surface at a tumor formation, does not reasonably provide enablement for any mutant of a cytoskeletal protein, a myosin protein and a NMMHC IIA protein which is antigenic, partly exposed on the cell surface and at the formation of a tumor mass. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

Nature of the Invention

Claims 5-9 are drawn to an antigen being partly exposed on the cell surface at the formation of a tumor mass, where the antigen is a cytoskeleton protein or a mutant thereof, or a myosin protein or mutant thereof, or non-muscular myosin heavy chain type A (NMMHC IIA) or mutant thereof.

Disclosure in the Specification

The interpretation of the specification is discussed supra with respect to lack of written support for mutant forms of the cytoskeletal proteins, myosin proteins and non-muscular myosin heavy chain type A proteins.

Status of the Prior Art/ Undue Experimentation

The Examiner was not able to identify prior art disclosure for mutant non-muscle myosin heavy chain type A proteins, according to the definition of the specification and which meet the limitations of Claim 1 (i.e., have any correlation with cell surface expression and carcinogensis). Thus the claims are not commensurate in scope with the enablement provided in the specification or the prior art. The specification does not support the broad scope of the claims which encompass any and all modifications to the amino acid sequence for NMMHC type A proteins because the specification does not disclose the following:

The general tolerance to modification and extent of such tolerance;

The specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; and

The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed antigens in manner a reasonably correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).f

Further protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411

(1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

Therefore, in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of molecules encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1 and 5-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Chiavegato et al. (Virchows Archiv. 426:77-86 (1995); cited on the PTO-form 892 of 1/11/07).

Claims 1 and 5-11 are drawn to an antigen being partly exposed on the cell surface at the formation of a tumor mass, where the antigen is a cytoskeleton protein or a mutant thereof, or a myosin protein or mutant thereof, or non-muscular myosin heavy

chain type A (NMMHC IIA) or mutant thereof, or a part of the NMMHC IIA, or a C-terminal domain of NMMHC IIA, or a C-terminal domain comprising residues 600-1960 of SEQ ID NO: 17 for NMMHC IIA, or C-terminal domains (peptides) comprising SEQ ID NOs: 20-22 of SEQ ID NO:17.

Chiavegato discloses expression patterns of non-muscle myosin heavy chain A (NMMHC-A) in neoplastic epithelial cells of the breast using the antibody, NM-G2, and that NMMHC-A appears as two different isoforms on electrophoresis (p. 80, Col. 1, ¶1). Fibroblasts present around neoplastic ducts in DCIS patient tissues were strongly positive for NMMHC-A (Fig. 7, p. 83, Col. 2). Thus, in fibrotic conditions including stromal reaction to mammary carcinoma, NMMHC-A is highly expressed. Because the claims are broadly drawn to any antigen (Claim 1), a cytoskeletal antigen (Claim 5) , a myosin antigen (Claim 6) and NMMHC-A (Claim 7), the NMMHC-A of Chiavegato reads on and therefore anticipates the claims. Further, the sequence of SEQ ID NO:17 for NMMHC-A (Claims 7-10) and C-terminal peptides of NMMHC IIA (SEQ ID NOs: 20-22) (Claim 11) are inherent to the NMMHC-A of Chiavegato. Finally, antigens comprising a part of NMMHC-A are encompassed by the isoforms for NMMHC-A as disclosed by Chiavegato.

For all of these reasons, the claims are anticipated by Chiavegato.

13. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 399257 A1 (Oregon Health Sci. U.; published 11/28/90; cited in the IDS of 4/27/05).

Claims 1-4 are broadly drawn to any antigen exposed on the surface of a cell at formation of any tumor mass, where a tumor cell is engrafted from a cultured cancer cell, and antigen expression is greater in the engrafted tumor.

EP 399257 A1 describes an antigen (L6) on the surface of tumor cells (XL-1 human lung tumor cells), and the transplantation of those cells into the brain of nude rats, where expression of the antigen is greater in vivo than in vitro.

For all of these reasons, the claims are anticipated by EP 399257 A1.

14. Claims 1 and 5-11 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/75067 (HYSEQ, INC; published 10/11/2001; cited in the IDS of 12/21/05) as evidenced by Saez et al. (PNAS 87:1164-1168 (1990); cited in the IDS of 12/21/05).

The interpretation of Claim 1 is discussed supra. Claims 5-11 are drawn to a cytoskeleton protein or a myosin protein or a NMMHC type A protein, where the antigen is the full length or a part of (e.g., C-terminal residues 600-1,960) the sequence for non-muscle myosin heavy chain type A of SEQ ID NO:17 and peptides (SEQ ID NOs: 20-22) derived from the C-terminal domain of SEQ ID NO:17. A NMMHC type A protein is a species of protein for the genus of cytoskeletal and myosin proteins.

WO 01/75067 A discloses the antigenic protein, NMMHC type 2, see SEQ ID NO: 32080 corresponding to the C-terminal domain of SEQ ID NO:17, which is

expressed in cancer cells, where the protein is antigenic, and where the peptides of SEQ ID NO:20-22 are comprised in the C-terminal domain of SEQ ID NO:17.

Saez teaches the entire sequence of NMMHC type A, see Figure 2, which represents the C-terminal domain of SEQ ID NO:17 and the peptides of SEQ ID NOs:20-22. The antigenic properties of the NMMHC type A protein are inherent to the protein.

For all of these reasons, the claims are anticipated by WO 01/75067 as evidenced by Saez.

Examiner's Comments Regarding the Scope of Claim 1

15. In view of the breadth of scope for Claim 1 which is drawn to any antigen exposed on the surface of a cell at formation of any tumor mass, the following references are noted:

a) MODAK et al., Cancer Research 61:4048-4054 (2001); cited in the IDS of 4/27/05;

b) WO 92/08131; published May 14, 1992; cited in the IDS of 4/27/05;

c) WO 02/057741; published July 25,2002; cited in the IDS of 4/27/05;

d) DIPPOLD et al., Cancer Research, 47:3873-3879 (1987); cited in the IDS of 4/27/05;

e) IMAM et al., Cancer Research 53:3233-3236 (1993); cited in the IDS of 4/27/05; and

f) OHUCHI et al., Surg. Today, 25:244-250 (1995); cited in the IDS of 4/27/05, because each of the references teaches antigenic proteins expressed on cells at tumor formation.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER